

What is Claimed Is:

1. A method for detecting a target molecule, said method comprising:

(a) bringing a plurality of electrodes supported by a semiconductor substrate
5 into proximity with a reaction medium comprising a sample suspected of containing
said target molecule, each of said electrodes comprising at least one target probe,

(b) selectively addressing a plurality of cells within said semiconductor
substrate

(i) to apply a stimulus to each of said electrodes to activate a
10 predetermined redox active moiety that is associated with an electrode, and

(ii) to detect, by means of said electrodes, corresponding responses
produced as a result of said activation of said redox active moieties,
the magnitude of said corresponding responses indicating the presence or absence of
said target molecule in said sample.

2. A method according to Claim 1 wherein said stimulus is voltage or
current and said corresponding response is current or voltage, respectively.

3. A method according to Claim 1 wherein said cell is addressed digitally.

4. A method according to Claim 3 wherein said stimulus is applied using an
analog bus, which cooperates with circuitry on or off said semiconductor substrate to
apply said stimulus to said electrode, and wherein said corresponding response is
detected using an analog bus, which cooperates with circuitry on or off said
25 semiconductor substrate to detect said corresponding response from said electrode.

5. A method according to Claim 3 wherein said stimulus is applied using a
digital bus, which cooperates with circuitry on or off said semiconductor substrate to
apply said stimulus to said electrode, and wherein said corresponding response is
30 detected using a digital bus, which cooperates with circuitry on or off said
semiconductor substrate to detect said corresponding response from said electrode, and
wherein said cell includes an analog-to-digital converter.

6. A method according to Claim 3 wherein said stimulus is applied using one of an analog bus or a digital bus with a digital-to-analog converter in said cell, which cooperates with circuitry on or off said semiconductor substrate to apply said stimulus to said electrode, and wherein said corresponding response is detected using
5 the other of an analog bus or a digital bus and an analog-to-digital converter in said cell, which cooperates with circuitry on or off said semiconductor substrate to detect said corresponding response from said electrode.

7. A method according to Claim 3 wherein said stimulus is stored in said
10 cell.

8. A method according to Claim 1 wherein said redox active moiety is incorporated into said target probe prior to step (a).

9. A method according to Claim 1 wherein said redox active moiety is incorporated into said target probe subsequent to step (a).
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10. A method according to Claim 4 wherein target probe comprises an oligonucleotide and said redox active moiety or precursor thereto is incorporated into
20 said target probe by means of a target dependent polymerase extension reaction.

11. A method according to Claim 1 wherein said detecting comprises the use of voltammetry or potentiometry.

12. A method for detecting a target molecule, said method comprising:
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 (a) bringing a plurality of electrodes supported by a semiconductor substrate into proximity with a reaction medium comprising a sample suspected of containing said target molecule, each of said electrodes comprising at least one target probe,
 (b) selectively applying electrical signals to each of said electrodes to
30 activate a predetermined redox active moiety that is associated with an electrode, and
 (c) detecting, by means of said electrodes, corresponding electrical signals produced as a result of said activation of said redox active moieties, the magnitude of said corresponding electrical signals indicating the presence or absence of said target

molecule in said sample.

13. A method according to Claim 12 wherein said selectively applied
electrical signals are voltages and said corresponding electrical signals are current or
5 potential difference or a combination thereof.

14. A method according to Claim 12 wherein said redox active moiety is
incorporated into said target probe prior to step (a).

10 15. A method according to Claim 12 wherein said redox active moiety is
incorporated into said target probe subsequent to step (a).

16. A method according to Claim 15 wherein target probe comprises an
oligonucleotide and said redox active moiety or precursor thereto is incorporated into
15 said target probe by means of a target dependent polymerase extension reaction.

17. A method according to Claim 12 wherein said each electrical signals are
selectively applied to said electrodes by means of a plurality of digital analog
converters, each of which is selectively electrically coupled to said electrodes.

20 18. A method according to Claim 12 wherein said electrical signals are
selectively applied to said electrodes by one or more analog converters which is
selectively electrically coupled to said electrodes.

25 19. A method according to Claim 12 further comprising (i) sending an
address to address decoders on said semiconductor substrate, said address decoders
being in communication with each of said cells, (ii) sending an item of numerical data to
storage means in each of a plurality of cells within said semiconductor substrate by
means of a data bus, said item of numerical data participating in the selection of a
30 voltage to be applied to said electrodes, and (iii) sending an address to address decoders
on said semiconductor substrate, said address decoders being in communication with
said storage means, whereby said item of numerical data is stored in said storage means
and electrical signals are selectively applied to each of said electrodes to activate a
predetermined redox active moiety that is associated with an electrode.

20. A method according to Claim 19 wherein an analog bus is employed and said item of numerical data identifies said analog bus that connects to said electrode.

21. A method according to Claim 12 wherein said detecting comprises the
5 use of voltammetry or potentiometry.

22. A method for detecting a target nucleic acid, said method comprising:

(a) bringing a plurality of electrodes supported by a semiconductor substrate into proximity with a reaction medium comprising a sample suspected of containing
10 said target molecule, each of said electrodes comprising at least one oligonucleotide probe,

(b) sending an item of numerical data to each of a plurality of cells within said semiconductor substrate by means of a data bus, said item of numerical data participating in the selection of a voltage to be applied to said electrodes,

15 (c) sending an address to address decoders on said semiconductor substrate, said address decoders being in communication with each of said cells, whereby electrical signals are selectively applied to each of said electrodes to activate a predetermined redox active moiety that is associated with an electrode, and

20 (d) detecting, by means of said electrodes, corresponding electrical signals produced as a result of said activation of said redox active moieties, the magnitude of said corresponding electrical signals indicating the presence or absence of said target nucleic acid in said sample.

23. A method according to Claim 22 wherein said selectively applied electric
25 signals are voltages and said corresponding electric signals are current or potential difference or a combination thereof.

24. A method according to Claim 22 wherein said redox active moiety is incorporated into said oligonucleotide probe prior to step (a).

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25. A method according to Claim 22 wherein said redox active moiety is incorporated into said oligonucleotide probe subsequent to step (a).

26. A method according to Claim 25 wherein said redox active moiety or precursor thereto is incorporated into said oligonucleotide probe by means of a target dependent polymerase extension reaction.

5 27. A method according to Claim 22 wherein said electrical signal is selectively applied to said electrode by means of a digital analog converter which is electrically coupled to said electrode and is associated with said cell.

10 28. A method according to Claim 22 wherein said electrical signal is selectively applied to said electrode by an analog converter which is electrically coupled to said electrode and is associated with said cell.

15 29. A method according to Claim 22 wherein said item of numerical data is representative of an electrical signal.

 30. A method according to Claim 22 wherein an analog bus is employed and said item of numerical data identifies said analog bus that connects to said electrode.

20 31. A method according to Claim 22 wherein said detecting comprises the use of voltammetry or potentiometry.

 32. A method according to Claim 22 wherein said at least one oligonucleotide binds a defined target nucleic acid sequence.

25 33. A method according to Claim 22 wherein said at least one oligonucleotide binds an undefined target nucleic acid sequence.

30 34. A method according to Claim 22 wherein said at least one oligonucleotide is part of a set of sequence specific oligonucleotides of predetermined length.

 35. A method for detecting a target nucleic acid, said method comprising:
(a) bringing a plurality of electrodes supported by a semiconductor substrate

into proximity with a reaction medium comprising a sample suspected of containing said target molecule, each of said electrodes comprising at least one oligonucleotide probe wherein each of said oligonucleotide probes comprises a redox active moiety,

5 (b) sending an item of numerical data to storage means in each of a plurality of cells within said semiconductor substrate by means of a data bus, said item of numerical data participating in the selection of a voltage to be applied to said electrodes,

(c) sending an address to address decoders on said semiconductor substrate, said address decoders being in communication with said storage means, whereby said item of numerical data is stored in said storage means and voltages are selectively
10 applied to each of said electrodes to activate said redox active moieties, and

(d) detecting, by means of said electrodes, corresponding current or difference in potential or a combination thereof produced as a result of said activation of said redox active moieties, the magnitude of said current or potential difference indicating the presence or absence of said target nucleic acid in said sample.
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36. A method according to Claim 35 wherein said voltages are selectively applied to said electrodes by means of a plurality of digital analog converters, each of which is electrically coupled to an electrode and is associated with a cell.

20 37. A method according to Claim 35 wherein said voltages are selectively applied to said electrodes by an analog converter which is electrically coupled to said electrode and is associated with said cell.

25 38. A method according to Claim 35 wherein said item of numerical data is representative of a voltage.

39. A method according to Claim 35 wherein an analog bus is employed and said item of numerical data identifies which analog bus connects to which electrode.

30 40. A method according to Claim 35 wherein said detecting comprises the use of voltammetry or potentiometry.

41. A method according to Claim 35 wherein said at least one oligonucleotide binds a defined target nucleic acid sequence.

42. A method according to Claim 35 wherein said at least one oligonucleotide binds an undefined target nucleic acid sequence.

43. A method according to Claim 35 wherein said at least one
5 oligonucleotide is part of a set of sequence specific oligonucleotides of predetermined length.

44. A method for detecting a target nucleic acid, said method comprising:

(a) bringing a plurality of electrodes supported by a semiconductor substrate
10 into proximity with a reaction medium comprising a sample suspected of containing said target molecule, each of said electrodes comprising at least one oligonucleotide probe,

(b) conducting a polymerase extension reaction to incorporate in each of said oligonucleotide probes, to which a target nucleic acid is bound, a redox active moiety or
15 precursor thereof,

(c) sending an item of numerical data to storage means in each of a plurality of cells within said semiconductor substrate by means of a data bus, said item of numerical data participating in the selection of a voltage to be applied to said electrodes,

(d) sending an address to address decoders on said semiconductor substrate,
20 said address decoders being in communication with said storage means, whereby said item of numerical data is stored in said storage means and voltages are selectively applied to each of said electrodes to activate redox active moieties associated with said electrodes, and

(e) detecting, by means of said electrodes, corresponding current or
25 difference in potential or a combination thereof produced as a result of said activation of said redox active moieties, the magnitude of said current or potential difference indicating the presence or absence of said target nucleic acid in said sample.

45. A method according to Claim 44 wherein prior to step (c) said electrodes
30 are washed.

46. A method according to Claim 44 wherein said polymerase extension reaction comprises having present in said medium nucleotide triphosphate analogs

comprising said redox active moiety or precursor thereto.

47. A method according to Claim 46 wherein said medium is incubated at temperature wherein said target nucleic acid hybridizes to respective oligonucleotide probes, which are extended by the addition of a respective nucleotide triphosphate analog.

48. A method according to Claim 44 wherein said precursor comprises a small organic molecule and said method comprises having present in said medium a binding partner for said small organic molecule, said binding partner comprising a redox active moiety.

49. A method according to Claim 44 wherein said precursor comprises a binding partner for a small organic molecule and said method comprises having present in said medium a small organic molecule comprising a redox active moiety.

50. A method according to Claim 44 wherein said at least one oligonucleotide binds a defined target nucleic acid sequence.

51. A method according to Claim 44 wherein said at least one oligonucleotide binds an undefined target nucleic acid sequence.

52. A method according to Claim 44 wherein said at least one oligonucleotide is part of a set of sequence specific oligonucleotides of predetermined length.

53. A method for identifying target nucleic acids in a sample, which comprises:

(a) applying said sample to a plurality of test sites, each of said test sites comprising an oligonucleotide probe attached to an electrode, each of said electrodes being part of a surface of an integrated circuit, each of said oligonucleotide probes being capable of specifically binding to a target nucleic acid molecular structure, such that each of said test sites has oligonucleotide probes which specifically bind to a different target molecular structure;

(b) incubating said sample on said test sites in the presence of a polymerase and nucleotide triphosphate analogs comprising a redox active moiety or a precursor thereof to extend each oligonucleotide probe, to which a target nucleic acid molecular structure is bound, and to associate said redox active moiety or precursor thereof with
5 each extended oligonucleotide probe, to which a target nucleic acid molecular structure is bound, with the proviso that, when said nucleotide triphosphate analogs comprise a precursor, a binding partner for said precursor is added wherein said binding partner comprises a redox active moiety;

(c) applying a voltage to each of said test sites by means of circuitry
10 associated with said integrated circuit, said voltage being sufficient to activate said redox active moiety associated with an electrode; and

(d) detecting by means of said integrated circuit a current or difference in potential or a combination thereof at each of said test sites, the magnitude of which is related to the presence of said target nucleic acids in said sample.

15 54. A method according to Claim 53 wherein said oligonucleotide probes are DNA probes or RNA probes.

20 55. A method according to Claim 53 wherein said detecting comprises the use of voltammetry or potentiometry.

56. A method according to Claim 53 wherein said integrated circuit comprises:

(a') a semiconductor substrate supporting a plurality of electrodes and

25 (b') a plurality of cells within said semiconductor substrate, wherein said integrated circuit comprises upon a single substrate:

(i) a plurality of digital analog converters, each electrically coupled to a respective electrode and each being associated with a respective cell,

(ii) address decoders in communication with each of said cells,

30 (iii) a data bus for delivering binary numerical data to each of said cells,

(iv) address buses for delivering addresses to said address decoders, and

(v) storage means in each of said cells for storing said numerical

data, said storage means being in communication with said digital analog converter in said cell; and wherein steps (c) and (d) comprise:

(a") sending binary numerical data to said storage means of each said cells by means of said data bus, said binary numerical data being representative of an electrical signal,

(b") sending addresses to said address decoders whereby said binary numerical data is stored in said storage means and electric signals are selectively applied to each of said electrodes by means of said digital analog converters to activate said redox active moiety associated with an electrode and

(c") detecting, by means of said electrodes, corresponding electrical signals produced as a result of said activation of said redox active moieties, the magnitude of said corresponding electrical signals indicating the presence or absence of said target molecule in said sample.

57. A method of testing a sample for the presence of target nucleic acids, said method comprising:

(a) applying said sample to an array of test sites in multiple locations on a surface of an integrated circuit, each site having oligonucleotide probes formed therein of known binding characteristics wherein the oligonucleotide probes in each test site differ from the oligonucleotide probes in other test sites in a known predetermined manner such that the test site location of oligonucleotide probes and their binding characteristics are known;

(b) treating each test site to which a target nucleic acid is bound, to extend the length of each oligonucleotide probe thereby incorporating an electronically responsive detector agent into each of said oligonucleotides;

(c) applying an electrical signal to each of said test sites by means of circuitry associated with said integrated circuit, said electrical signal being sufficient to activate said electronically responsive detector agent associated with an electrode; and

(d) detecting by means of said integrated circuit a change in electronic properties of the test sites resulting from the binding of target nucleic acid to lengthened oligonucleotide probes in the test sites by detection circuitry coupled to individual test sites to determine which target nucleic acid has bound to a test site; whereby the presence of a multiplicity of different target nucleic acids in the sample is detected.

58. A method according to Claim 57 wherein said oligonucleotide probes are DNA probes or RNA probes.

59. A method according to Claim 57 wherein said detecting comprises the use of voltammetry or potentiometry.

60. A device comprising:

- (a) a semiconductor substrate,
- (b) at least one surface having associated therewith a redox active moiety,
- (c) an electrode adjacent said surface and supported by said semiconductor substrate,
- (d) a cell within said semiconductor substrate,
- (e) a digital analog converter to which said electrode is electrically coupled, said digital analog converter being associated with said cell,
- (f) an address decoder in communication with said cell,
- (g) a data bus for delivering an item of numerical data to said cell,
- (h) an address bus for delivering an address to said address decoder, and
- (i) means for monitoring said surface.

61. A device according to Claim 60 wherein said means for monitoring comprises an analog bus.

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